Remarks

Claims 54-123 are pending in this application. Claims 54, 68, 78, 92 and 107 have been amended to remove the previously added claim language without acquiescing to the propriety of the rejection, solely to expedite the prosecution of this case. Applicants respectfully request that the Examiner reconsider and withdraw the outstanding rejections discussed below.

Claim Rejection Under 35 U.S.C. § 112, First paragraph

Claims 54-123 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. (Office Action, page 2.)

In view of the amendments to Claims 54, 68, 78, 92 and 107 that remove the "added language", Applicants believe this rejection is moot and should be withdrawn.

Claim Rejection Under 35 U.S.C. § 103(a)

Claims 54-123 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Huo *et al.* (Huo) (U.S. Patent No. 5,922,535) in view of Chenchik *et al.* (Chenchik) (U.S. Patent No. 5,962,271). (Office Action, page 3.)

The Examiner maintains that Huo discloses several embodiments of the invention, including biotinylated poly-T primers that include a rare restriction site at its 5' end, and that after cleavage, at least one biotinylated nucleotide is retained on the 3' of the cleavage site.

The Examiner adds that Huo discloses that the cut site is filled in with biotinylated nucleotides. (Office Action, page 3.) The Examiner acknowledges that Huo covers steps (a)-(c) of claim 54, but not step (e). (Office Action, page 4, lines 1-2.) The Examiner alleges that when Huo's teachings are combined with Chenchik's teachings, the instant invention would result. Applicants respectfully disagree with the Examiner's conclusions for the reasons discussed below and traverse this rejection.

Huo

Huo teaches a method to detect sequence differences between two or more nucleic acid populations (for e.g.: mRNA, genomic DNA, alternatively spliced cDNAs, etc.) by hybridizing different populations of nucleic acids to form mismatch-containing duplexes. Huo uses biotinylated primers comprising rare restriction sites at the 5' end for standard cDNA synthesis (*see* Huo at column 12, lines 9-24). The primers are biotinylated by using biotinylated poly T, or, by restriction enzyme cleavage of the primer creating overhangs, which are then filled in with a DNA polymerase and biotinylated nucleotides (*see* column 13, lines 12- 26 and 40-52). The biotinylated nucleotides facilitate attachment of synthesized cDNA or RNA: DNA hybrids to immobilizing supports. A point to note is that the restriction digestion and biotinylation of the primers would have occurred before the immobilization step. Huo, either chemically cleaves or uses RNAse A (for RNA-DNA cleavage) to cleave the mismatched base pair from the column (see all figures and column 12, lines 58-61). Chemical cleavage is performed under denaturing conditions (e.g. with

NaOH) which can damage DNA. Huo does not use restriction enzymes to cleave the cDNA or RNA-DNA hybrids fragments from the solid support.

Chenchik

Chenchik teaches cDNA synthesis using primers that comprise rare restriction sites, which upon digestion of the cDNA with restriction enzymes, facilitates its cloning into cloning vectors (*See* Chenchik at column 9, lines 17-25 and for e.g.: Fig. 3.2, 4.1, etc). Chenchik does not teach binding of the cDNA to a the hapten-cDNA molecule complex, nor the release of cDNA from the complex using restriction enzymes.

The claimed invention

The invention, as defined by claim 54, is drawn to methods of making one or more cDNA molecules, comprising the steps of:

(a) combining one or more RNA molecules with (i) one or more polypeptides having reverse transcriptase activity and (ii) at least one primer adapter nucleic acid molecule, wherein the at least one primer-adapter nucleic acid molecule comprises one or more ligands and one or more cleavage sites, to form a mixture;

(b) incubating the mixture under conditions sufficient to make one or more double stranded cDNA molecules, wherein one or more of the cDNA molecules comprise at least one primer-adapter nucleic acid molecule;

(c) contacting one or more of the cDNA molecules with at least one hapten to produce one or more hapten-cDNA molecule complexes;

(d) cleaving one or more of the complexes with not more than one enzyme, wherein said enzyme cleaves one or more of the complexes at one or more cleavage sites within the primer-adapter, to produce one or more cleaved cDNA molecules; and

(e) inserting or ligating one or more of the cleaved cDNA molecules into one or more vectors.

Applicants note that methods which are the subject of the claims presented herein involve an ***enzymatic*** cleavage step the cDNA from a hapten-cDNA molecule complex. Thus, enzymatic cleavage is used to release the cDNA molecules from the hapten-cDNA molecule complex.

Arguments

Applicants respectfully submit that a *prima facie* case of obviousness has not been established in this instance because all the claim elements of the present invention have not been taught by either reference alone, or their combination. Central to all of the Examiner's arguments is the alleged assertion that the Huo reference teaches enzymatic cleavage like in the Applicants' invention. Applicants respectfully disagree.

In particular, Huo cleaves the primers (not cDNA) with restriction enzymes resulting in *primers with overhangs* before binding the cDNA to the solid support (*see* Huo, column 13, lines 12- 26 and 40-52). Applicants note that the Examiner has acknowledged that Huo discloses that the cut site is filled in with biotinylated nucleotides. (Office Action, page 3.) On the other hand, using claim 54 as a point of reference, step (d) recites: "cleaving one or more of the complexes with not more than one enzyme, wherein said enzyme cleaves one or

more of the complexes at one or more cleavage sites within the primer-adapter, **to produce one or more cleaved cDNA molecules**" (emphasis added). Moreover, the disclosure of Chenchik does not make up for the lack of teaching of cleaving immobilized cDNAs with restriction enzymes. Therefore, all the claim elements are not disclosed by the cited art, either alone or in combination and in fact, skilled artisans, considering the cited references as a whole, could not have arrived at the instantly claimed invention.

Thus, a *prima facie* case of obviousness has not been established. Applicants thus respectfully request that the Examiner reconsider and withdraw the rejection of claims 54-123 under 35 U.S.C. § 103(a).

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider and withdraw all presently outstanding rejections. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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